

Spontaneous emergence of catalytic cycles with colloidal spheres

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Colloidal particles endowed with specific time-dependent interactions are a promising route for realizing artificial materials that have the properties of living ones. Previous work has demonstrated how this system can give rise to self-replication. Here, we introduce the process of colloidal catalysis, in which clusters of particles catalyze the creation of other clusters through templating reactions. Surprisingly, we find that simple templating rules generically lead to the production of huge numbers of clusters. The templating reactions among this sea of clusters give rise to an exponentially growing catalytic cycle, a specific realization of Dyson's notion of an exponentially growing metabolism. We demonstrate this behavior with a fixed set of interactions between particles chosen to allow a catalysis of a specific sixparticle cluster from a specific seven-particle cluster, yet giving rise to the catalytic production of a sea of clusters of sizes between 2 and 11 particles. The fact that an exponentially growing cycle emerges naturally from such a simple scheme demonstrates that the emergence of exponentially growing metabolisms could be simpler than previously imagined.

catalytic cycles | DNA-coated colloids | metabolism | templating

he origin of life is usually associated with self-replication, the ability of an entity to create copies of itself (1). Thus inspired, there have been many efforts in recent years aimed at creating artificial systems with self-replicative capacity. These are typically inspired by the linear chain mechanism of DNA. However, living systems are more than individual entities that can replicate themselves. Dyson (2) and Oparin (3) argued that a more critical aspect of living systems is the creation of a metabolism, a complex cascade of chemical reactions that together are able to accomplish more than any single chemical reaction can do on its own. Using a simple mathematical model, the so-called "garbage bag model," Dyson presented a scenario through which such a complex metabolism could arise spontaneously. His idea is that a random set of catalysts will catalyze arbitrary chemical reactions in a nonsynergistic fashion. However, if each catalyst is more likely to function when there are others that are synergistic with it, then there is a critical amount of cooperativity above which metabolic cycles spontaneously emerge. This idea has been explored through abstract simulations (4). In a similar spirit, Kauffman and coworkers have shown that if the probability of one species catalyzing the formation of another is above a threshold, then catalytic cycles naturally emerge (5-7).

Whether this scenario can naturally occur in practice remains obscure. The fundamental question is to determine how likely it is for a soup of interacting catalysts to self-organize into an exponentially growing catalytic cycle. How special do the interactions between the different components need to be for spontaneous exponentially growing catalytic cycles to emerge? In this work, we present an explicit demonstration of a set of interactions in which exponentially growing catalytic cycles naturally emerge. This set of interactions models a realizable physical sys-

tem, colloidal spheres interacting with time-dependent specific interactions, in which particle clusters can template each other. The emergence of exponentially growing catalytic cycles depends on particle valences in the templating process.

We consider colloidal particles having stickers distributed uniformly over their surface. These stickers cause short-ranged, specific interactions between particles, with a programmable binding strength between pairs of particles. We have recently shown that this system has the potential of allowing high-yield equilibrium self-assembly of large structures, up to 1,000 particles (8). Classical experiments showed that DNA-based specific interactions allow assembly of crystals of nanoparticles (9-12). More recently, efforts for self-assembly at the colloidal scale have begun to bear fruit (12-18). To achieve the exponentially growing catalytic cycles of the current study, we find that it is necessary to use time-dependent interactions between the particles, whose strength can be modulated over a programmable timescale. Schemes for time-dependent interactions based on DNA hybridization exist (19), and there is already an experimental realization of a form of time-dependent interactions (20), with more under development. We will see in what follows that the timescale of the interactions plays an essential role in determining the nature of the catalytic cycles that are produced in the reactions.

Results

We define a "cluster" as a rigid structure in which any continuous deformation costs energy and in which N particles interact

Significance

Biological systems inspire a new paradigm for material synthesis, aiming to design materials that emulate living systems, providing both functionality and self-replication. Colloidal particles endowed with specific interactions provide a particularly promising approach for realizing this vision. Here, we consider a set of colloidal spheres with specific, time-dependent interactions and demonstrate that the interactions can be designed so that clusters of particles create other clusters through templating reactions. Surprisingly, simple templating rules generically give rise to the production of a sea of clusters of various sizes. The sea of clusters grows exponentially in a catalytic cycle. This is a specific realization of Dyson's notion of an exponentially growing metabolism, emerging naturally from a simple scheme.

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through specific short-range interactions. On the one hand, a cluster is characterized by its geometry: It has been shown that for N < 6, for each N, there is only one rigid structure, and for $N \geq 6$, there are multiple rigid structures (2 for N = 6, 5 for N = 7, 13 for N = 8, and so on) (21, 22), with nearly 10^6 at N = 14 (23) (Fig. 1A). On the other hand, a cluster is characterized by the species of particles that comprise it, where the species of two particles determines the specific interaction between them. The number of different species of particles is not necessarily the same as N. It has been previously established how specific interactions can be chosen for any given geometry (8, 16, 24, 25) and how self-assembly yield of clusters depends on the chosen interactions (8, 24). In the present work, we do not consider self-assembly of clusters in a bath of particles (8, 16, 25, 26); however, our ability to enumerate cluster geometries and choose interactions to stabilize any desired cluster is a critical ingredient for the discoveries reported here. Instead, here we focus exclusively on formation of a cluster through templating from another cluster, which is a form of catalysis. Template-based catalysis is common in biology (27, 28) and offers a different route to increasing the production rate of a structure in exchange for energy expenditure.

Templating Catalysis. To define our model system, we select one specific cluster of size $N=N_0$, termed here the "parent catalyst," and choose from the earlier enumerations (8, 24) the particle species and interactions that make it the only ground state of N_0 particles. In this work, however, the particle number is not fixed, and instead of the self-assembly process, we consider exclusively templating catalytic reactions as means of creating clusters. The choice of interactions, therefore, only guarantees that the parent catalyst is indeed a rigid configuration of particles. The templating process, as will be defined shortly, is based on monomers attaching to clusters, which implies that particle valence is important in catalysis. The choice of allowed valences is, in principle, independent of the already introduced interaction rules.

We will present in detail the catalytic system arising when the parent catalyst is a specific $N_0=7$ cluster (Fig. 1 B and CI), and then show that the presented behavior is generic in our model, occurring in a multitude of parent catalysts with sizes $N_0=6$ to $N_0=8$. To define the templating process and illustrate the significance of particle valence, we proceed by describing a specific templating catalysis reaction in which the parent catalyst templates an octahedron cluster (N=6).

A templating reaction occurs in three distinct steps, with our example illustrated in Fig. 1B: First, monomers from the bath bind to the surface of the catalyst cluster, with the bound monomers forming bonds with each other. In the second step, the network of bound monomers dissociates from the original cluster. In the third step, the dissociated network folds into a new cluster. To catalyze formation of a specific cluster, it is necessary to specify the rules for binding monomers to a given particle of the parent catalyst (i.e., specify the particle valence). Our previous work (29) showed that efficient autocatalysis of the octahedron, with at most one monomer binding to a parent particle (valence 1), required including an additional cluster in the reaction. Here, we consider templating from a single catalyst, without limiting the particle valence. To catalyze the formation of the octahedron from the $N_0 = 7$ parent catalyst, it turns out that we must adopt the following rule—although particle species labeled 1-6 can only bind one monomer from the bath, particle species 7 can bind two monomers from the bath (Fig. 1C).

The reason for this can be seen in our algorithm for finding possible catalysts for a given cluster: In Fig. 1 C1, the "interaction matrix" shows which particle species in the catalyst can contact each other through their specific interactions. In Fig. 1 C2, the matrix shows which particles within the octahedron are in contact. For the $N_0 = 7$ parent cluster to catalyze the octahedron, we must find a submatrix of the interaction matrix that matches the contacts in the octahedron. Fig. 1 C3 shows that this can only happen if particle species 7 has valence 2, while the other particles have valence 1. Using this algorithm, we searched through all geometries and compositions

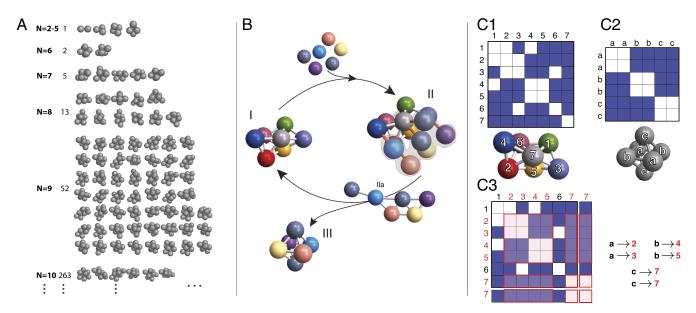


Fig. 1. (A) Landscape of different rigid structures that can be formed out of N particles. (B) Templating scheme for making an octahedron (III) from an $N_0 = 7$ cluster (I). A catalyst particle can bind a monomer of complementary species, which are differently colored. (C1) Interaction matrix for the $N_0 = 7$ cluster. Blue entries denote attraction between particle species. The set of complementary species has the exact same interaction rules. (C2) Contact matrix for the octahedron. Blue entries denote particles in contact. (C3) How the templating in B is possible: The contacts in the octahedron (C2) have to be allowed by the interactions of particle species in the $N_0 = 7$ cluster (C1). This can only be realized (shaded red with particle assignments on bottom) if one of the particles (species 7) has valence 2.

in our landscape (8, 21, 22, 24) and found multiple parent clusters that can efficiently catalyze the octahedron: The discussed parent catalyst is the only one with $N_0 = 7$, and multiple parents with $N_0 > 7$ can carry out the reaction efficiently (SI Text and Fig. S1). There is nothing special about the reaction in which the octahedron is the target; however, the choice of having particle valence larger than one strongly impacts the totality of catalytic reactions for a given parent catalyst, as we will discuss below.

The reactions of template-driven catalysis require timedependent bond strengths: The bond strengths of the monomers binding to the catalytic cluster must weaken in time, whereas the bonds between bound monomers must strengthen in time. The dissociation timescale of the network of bound monomers is set by the timescale of the weakening bonds. By varying this timescale, it is possible to change the size of the dissociated network of monomers and hence the size of the catalyzed cluster. This process is in spirit similar to the time-dependent type of enzyme catalysis, which has been established as a common type of catalysis in biology (28). In our simulations, we implement this varying timescale by triggering the dissociation event based on the number of bonds within the monomer network. We choose the necessary number of bonds for triggering dissociation from a distribution, where moving the distribution peak toward, e.g., larger numbers corresponds to a longer dissociation timescale (SI Text and Fig. S2).

When the interactions are realized by DNA stickers, the monomer-catalyst binding involves complementary strands, so that for each particle species in the parent, there is a complementary particle species that can bind to it. The complementary species interact among themselves in the same way as the original species do. The catalytic system of the $N_0 = 7$ parent catalyst (Fig. 1 C1) is therefore defined to have double the number of species, i.e., 14 species (Fig. 24). We now proceed to test in detail the performance of the $N_0 = 7$ parent catalyst, using dissipative particle dynamics (DPD) techniques introduced previously for colloidal particles with stickers (8, 29). Our simulation contains colloidal spheres of diameter d, with an interaction range of 1.05d. The particles are immersed into a DPD solvent of smaller particles. We simulated systems with 512 colloidal particles, out of which 7 comprise the parent catalyst. Simulations are run at a fixed temperature with a volume fraction of colloids $\phi_{coll} = 0.01$. Fig. 2B shows a particular event of the parent cluster producing an octahedra in a simulation.

Emergent Catalytic Reactions. Although Fig. 2*B* demonstrates that the $N_0 = 7$ parent catalyst indeed effectively templates octahedra, a close examination of the simulations demonstrates that the cluster is also capable of templating other clusters. In turn, the clusters that are templated from the parent $N_0 = 7$ catalyst can themselves template even more clusters. The rich templating capability becomes apparent as we increase the number of monomer bonds necessary for dissociation event and thereby favor larger catalysis products. Fig. 2C shows a snapshot from a simulation, highlighting a few examples of clusters and nonrigid structures.

The root cause of the degenerate structures that are produced is the valence-2 particle in the $N_0 = 7$ parent catalyst. Without this valence-2 particle, only some clusters with < 7 particles can be templated (SI Text and Fig. S3). However, the degeneracy causes an enormous zoo of clusters to be produced by the templating reactions. To enumerate the set of possible rigid clusters that can be produced starting from the $N_0 = 7$ cluster, we take our database of cluster geometries up to 14 particles (21–23) and ask which of these geometries can be realized by using the interaction matrix of the parent $N_0 = 7$ catalyst (Fig. 1 C1), where multiple copies of the valence-2 particle are allowed (particle species 7). There are 100 different geometries that are consistent with this interaction matrix, from N=2 to N=11 particles. These give rise to a total of 176 different clusters, because some of the geometries have multiple colorings (i.e., some geometries can be constructed using different combinations of particle species). Of the 176 clusters, 135 have >5 particles, and we focus on these.

We next ask which of the 135 clusters are capable of templating each other. Note that from here on, for simplicity of presentation, we consider clusters with complementary colorings to be one and the same; i.e., a pair of complementary particle species is regarded as a single species. This simplification does not affect any of our results and conclusions (SI Text). Fig. 3 shows a directed graph, where each of the 135 nodes corresponds to a rigid cluster. A (directed) edge between two nodes indicates

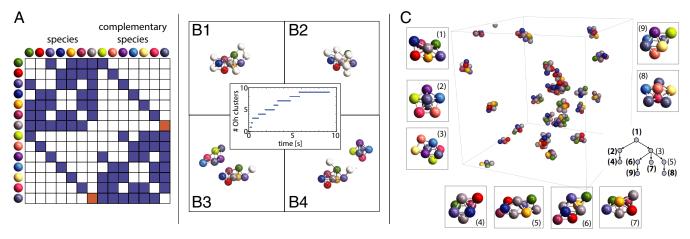


Fig. 2. (A) The interaction matrix shows that the mutual interactions among the catalyst cluster particles (the first seven rows/columns) are identical to the ones among their complementary species (the last seven rows/columns). Each particle species can bind its complementary species (off-diagonal seven by seven blocks). Orange entries mark the only interactions with valence 2. (B) Simulation of catalysis of octahedra from the $N_0 = 7$ parent catalyst. Particles in the catalyst are colored according to their interaction matrix, with the particles bound from the bath colored white (unbound particles and solvent particles are omitted for clarity). (B1-B4) Snapshots of an octahedron being formed. (B, Inset) Plot of the number of octahedra as function of time obtained in a simulation. (C) Snapshot of simulation started with a single $N_0 = 7$ catalyst (labeled 1), where all generated clusters were allowed to template other clusters. A few selected clusters (labeled 2-9) are marked, with the sequence of them getting templated shown on the right. Only clusters 3 and 5 are nonrigid structures. Clusters 3 and 6 have eight particles, cluster 5 has nine particles, and the rest have seven particles.

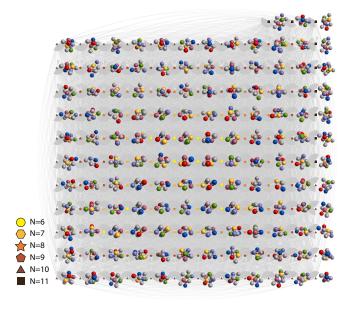


Fig. 3. Directed graph showing the templating connections between all clusters with >5 particles, realized by using the interaction matrix of the $N_0 = 7$ parent catalyst. There are 135 clusters in total.

that the initial cluster can template the target one. There are 8,057 pairs of connected clusters in the graph, so the probability of a connection between any two clusters is $\sim 90\%$. This percentage is higher than the critical value predicted by Kauffman above which catalytic cycles emerge from a reactive graph (5,6). Indeed, there are many cycles within our graph, an example of which is shown in Fig. 44.

To make the structure of the cycles visible, Fig. 4B reorganizes the graph in Fig. 3, grouping clusters by their size and coloring. For example, to generate a cycle with a N=11 cluster starting from the parent $N_0=7$ catalyst, we need to template a type of N=8 cluster (8 possibilities out of 24 clusters), which then templates a type of N=9 cluster (31 possibilities out of 37 clusters). There are $>1.7\times10^6$, 1.0×10^7 , 6.2×10^8 cycles of length 3, 4, 5, respectively. The parent $N_0=7$ catalyst is involved in $\approx 15\%$ of the average number of cycles per cluster. The largest cycle we found has size 83 and involves the parent catalyst.

Exponential Growth of Catalytic Cycles. Given this web of templating possibilities between the different clusters (Figs. 3 and 4B), what is the outcome when a $N_0 = 7$ catalyst is placed in a monomer bath? To answer this, let $\mathbf{c}(t)$ be a vector of probabilities, where $c_i(t)$ is the normalized concentration of the i^{th} cluster. Then,

$$\frac{d\mathbf{c}}{dt} = \mathbf{M}\mathbf{c},\tag{1}$$

where **M** is the matrix of first-order production rates between the different clusters, with M_{ij} representing the rate at which the j^{th} cluster templates the i^{th} cluster.

Now, M_{ij} can only be nonzero if the corresponding edge in the directed graph (Figs. 3 and 4B) is nonzero. The magnitude of M_{ij} is set by kinetic considerations: A templating reaction requires that all of the templated particles diffuse to the surface of the catalyst and then dissociate together once enough bonds between the particles are formed. The critical parameter is the timescale of dissociation, $\tau_{\rm dis}$, the length of time the templating particles are allowed to stay bound to the catalyst before they dissociate. The number of particles that template before dissociation increases with increasing $\tau_{\rm dis}$, leading to a preference for larger clusters. In contrast, if $\tau_{\rm dis}$ is short, templating larger clusters is impossible, and the catalysts only produce small clusters.

A reasonable model chooses $au_{
m dis}$ so that templated clusters of a given size are favored, and then both larger and smaller clusters are disfavored. We model this by choosing the value of each matrix element of M, i.e., the value of kinetic rate for each templating reaction, which is inversely proportional to the corresponding $au_{
m dis}$. Given a matrix M, what is the dynamics of Eq. 1, assuming that we start from a single instance of the $N_0 = 7$ catalyst? If **c** has K components, then Eq. 1 has K eigenmodes, namely, solutions C_i^{α} that grow/shrink exponentially when Re[λ^{α}] is positive/negative, where λ^{α} is the corresponding eigenvalue. When we choose the kinetic rates to vary weakly (SI Text), the spectrum corresponding to our model is shown in Fig. 5A. We sort the eigenvalues so that $Re[\lambda^1]$ is the smallest and $Re[\lambda^K]$ is the largest. The same figure shows the spectrum for a different choice of kinetic rates, drawn from an exponential distribution, where kinetic rates for production of the largest clusters happen to be relatively increased (SI Text). In both cases, the λ^K is real and $\lambda^K \gg \text{Re}[\lambda^{\alpha}]$ for $\alpha < K$, and we find this to be a robust feature under variation of kinetic rates. This is consistent with the Perron-Frobenius theorem, which guarantees

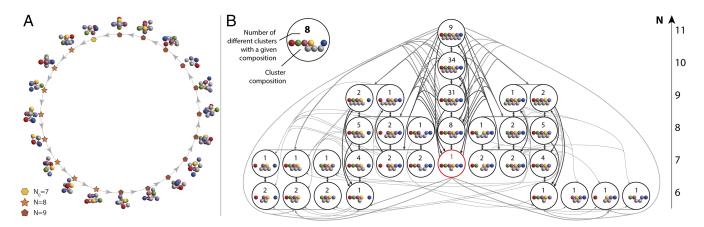


Fig. 4. (A) An example of emergent catalytic cycle that includes the $N_0 = 7$ parent catalyst. (B) The reorganization of the directed graph in Fig. 3, where clusters are grouped by their number of particles (N) and by the species of each of their particles. A directed edge from a group of clusters (a circle) to another group means that all clusters in the former can template all clusters in the latter group. When the edge has an endpoint on a horizontal line that connects several circles, it represents multiple edges to each of those circles. The group to which the $N_0 = 7$ cluster belongs is marked by a red circle.

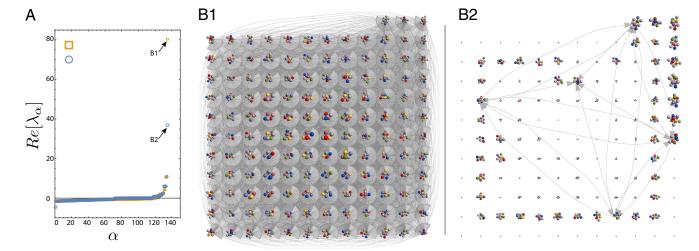


Fig. 5. (A) The spectrum corresponding to the kinetic equations for templating, with eigenvalues λ^{α} , $\alpha=1\dots$ 135. The two spectra belong to two different choices of kinetic rates for templating: slightly varying rates (squares), and rates chosen from an exponential distribution (circles) (Exponential Growth of Catalytic Cycles). The fastest growing eigenmode for each choice of kinetic rates corresponds to the marked eigenvalue. (B1) The fastest growing mode for slightly varying kinetic rates of templating. The size of the cluster image is proportional to the concentration of the cluster. Directed connections show the templating relations. (B2) The fastest growing mode for kinetic rates chosen from an exponential distribution (Exponential Growth of Catalytic Cycles). The size of the cluster image is proportional to the concentration of the cluster. We show the mutual catalytic relations only for five clusters.

a maximal real eigenvalue for a matrix representing a strongly connected graph (30). In our example, the 83 clusters from the largest cycle form the largest strongly connected component and lead to the maximal real eigenvalue. At long times, the solution will be dominated by the eigenmode corresponding to the largest exponential term,

$$\mathbf{c}(t) \sim \beta \mathbf{C}^K e^{\lambda^K t},$$
 [2]

given that the projection, β , of the initial condition onto this eigenmode is nonzero. We indeed find that for the initial condition with only the $N_0 = 7$ cluster in the bath, there is robustly a significant overlap with the C^K eigenmode.

The structure of the eigenmode \mathbf{C}^K is sensitive to the choice of kinetic rates, even though the existence of a dominating λ^K is robust. The clusters involved in the longtime solution are shown in Fig. 5B for our two different choices of kinetic rates. When all kinetic rates are similar, the solution involves clusters of all sizes, preferring slightly the smaller ones because these can be templated by both small and large clusters, whereas the converse does not hold. When kinetic rates are uneven, as in our second choice, only a subset of clusters is involved in the long-term solution, representing a smaller set of catalytic cycles, as shown in Fig. 5 *B2*.

Generality of Emergent Cycles in Colloidal Catalysis. The question arises of how general is the behavior of the catalytic system based on the $N_0 = 7$ parent catalyst? To answer this, we analyzed the catalytic systems arising from each cluster between $N_0 = 6$ and $N_0 = 8$ as the parent catalyst. Allowing a single (any) particle of the fixed parent (a total of 105 parents) to have valence 2 results in 716 different catalytic systems. We generate the directed graph for each, just as in Fig. 3, checking for geometries from N=6 to N = 10 (a total of 333 geometries). Compared with the described $N_0 = 7$ parent, we find that dozens of other parent catalysts generate catalytic systems that are at least as large and have as big a maximal cycle (Fig. 6, blue bars). We note that throughout the entire histogram (Fig. 6, blue bars), one can find catalytic systems based on any number of particle species; the minimum is 4 species (when the parent has 2), and the maximum is 16.

In contrast, in the case when all particles have valence 1, the catalytic systems generated in the same way as above are drastically smaller; there are very few cycles, and all of them contain <6 clusters (Fig. 6, gray bars). Because of valence constraint, a cluster cannot template a larger one, so that cycles can occur only among clusters with the same N. Our example of $N_0 = 7$ parent catalyst illustrates this: With valence set to 1, we find no catalytic cycles (SI Text), in stark contrast to the case with valence 2.

Discussion

Our exponentially growing catalytic cycles appear to be an explicit realization of Dyson's classical mechanism (2) for the emergence

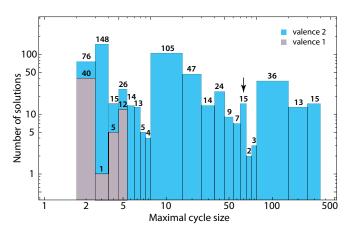


Fig. 6. Histograms for the 716 different valence-2 catalytic systems (blue) and 105 different valence-1 catalytic systems (gray), according to their largest catalytic cycle. The number above the bar counts the number of systems having the maximal cycle size within the range of the bar. Each catalytic system is generated by parent cluster of size $N_0 = 6, 7$ or 8, with a single (any) particle species allowed valence 2 (blue) or all having valence 1 (gray). In each system we are considering only different geometries of clusters with N between 6 and 10. Systems without cycles >1 (i.e., the only cycles are self-catalysis) were omitted from the histogram (125 and 47 for valence 2 and 1, respectively). The arrow marks the bin in which lies the $N_0 = 7$ catalytic parent discussed in detail.

of catalytic cycles. Instead of a single proliferating entity, our system results in exponentially growing catalytic cycles, which is reminiscent of a metabolism. Were the reactions to occur in a cell volume that itself divided in response to, e.g. the amount of one of the clusters in our cycle, we would have a natural mechanism for an exponentially growing catalytic cell cycle.

Whereas previous models realizing Dyson's metabolism are abstract (4–6), without specific physical realization, the present construction demonstrates that it is surprisingly easy for a templated set of reactions to give rise to an exponentially growing catalytic cycle. Our only caveat is that the specific nature and properties of the catalytic cycle are emergent properties of the programmed interactions and cannot easily be directly designed. The only special aspect of the system studied here is that we have a complete characterization of the energy landscape of the colloidal particles, and therefore are able to easily make the design choices for a templated catalytic reaction to emerge. However, we see no reason why similar phenomena could not emerge from other soft-matter systems, in particular, polymers or gels (31). As but one example, it is interesting to contemplate whether a system of RNA strands might be designed to lead to an exponential catalytic cycle.

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We note that the basic ingredients required to experimentally realize our system are becoming available. Controlled valence of isotropic mesoscale particles has been demonstrated (18, 32). The interaction among monomers needs to strengthen in time, so that they do not aggregate in solution, but do bind to each other during time they are attached to the template. We believe that the dissociation from the template could be induced by the very process of bonding among attached monomers (33) and/or by weakening in time of the monomer-template bonds (19), both of which require consumption of energy. The weakening and breaking of monomer-template bonds might be controlled by an externally imposed (i.e., day-night) cycle for these bonds (31, 34, 35), which could set the disassociation timescale. A first step toward time-dependent interactions has been realized between nanoparticles by using complex strand-displacement reactions that rely on a DNA fuel source (20, 36).

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